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10/567,406	10/19/2006	Birgitte Holst Lange	LANGE6A	2286

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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,406	LANGE ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,13-20,22,23,27-29,31,33-35,37,39,40 and 43-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-6,13-20,22,23,27-29,31,33-35,37,39,40 and 43-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendments to Non-final rejection filed on February 04, 2008 and supplemental amendment filed on April 02, 2008 are acknowledged. New claims 45-52 have been added. Claims 1-3, 5, 6, 13-20, 22-23, 27-29, 31, 33-35, 37, 39, 40, 43-44 and 45-52 are pending in this application. Applicant elected with traverse Group I and elected species of SEQ ID NO:1 in the reply filed on August 23, 2007. The restriction requirement was deemed proper and made FINAL in the previous office action. Under further consideration, it was determined that claim 5 is part of the elected species, thus claim 5 is rejoined. Claims 1-3, 5-6, 13-20, 22-23, 27-29, 31, 33-35, 37, 39, 40 and 43-52 are examined on the merits in this office action.

Withdrawn Objection

1. Objection to title is hereby withdrawn due to Applicant's amendment to the title to "PROPHYLAXIS AND TREATMENT OF CANCER CACHEXIA".

2. Objection to claim 1 is hereby withdrawn due to Applicant's amendment and persuasive argument.

Withdrawn Rejection

3. Rejection of claims 1 and 39 under 35 U.S.C. 112, second paragraph, is hereby withdrawn due to Applicant's amendment to the claims.

4. Rejection under 35 U.S.C. 112, lack of enablement, is hereby withdrawn due to Applicant's amendment to the claims.

Maintained and Modified Rejection

35 U.S.C. 112, 1st

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2, 6, 15-20, 22-23, 27-29, 31, 33-35, 37, 39, 40, 43-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

7. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

8. Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

9. The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court

determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

10. In the instant case, the claims are drawn to a method for prophylaxis or treatment of cancer cachexia and a method for stimulation of appetite in an individual in need thereof, comprising administration to said individual a ghrelin-like compound or a pharmaceutically acceptable salt thereof having the structure defined by formula I, wherein said ghrelin-like compound or pharmaceutically acceptable salt thereof is 27-28 amino acids in lengths, with the proviso that said ghrelin-like compound is at least 80% homologous to SEQ ID NO: 1 and at least 90% homologous to SEQ ID NO:1. Furthermore, claims 1 and 39 recite "wherein the ghrelin-like compound comprises a structure defined by formula I, Z^1-$(X^1)_m$-(X^2)-$(X^3)_n$-Z^2, wherein...each X^1 is independently selected from an amino acid...each X^3 is independently selected from an amino acid...m is an integer in the range of from 1-10, n is an integer in the range of from 15-35. Furthermore, claim 49 is drawn to the method wherein the amino acid sequence of the ghrelin-like compound differs from that of human ghrelin solely by (1) N- or C-terminal extensions, (2) N- or C-terminal truncation, or (3) conservative amino acid substitutions. The generic statements ghrelin-like compounds and 27-28 amino acids in lengths, with the proviso that the ghrelin-like compound is at least 80% homologous to SEQ ID NO:1 and at least 90% homologous to SEQ ID NO: 1, synthetic amino acids, bulky hydrophobic group, Z^1-$(X^1)_m$-(X^2)-$(X^3)_n$-Z^2, and N- or C-terminal extensions, truncation, or conservative amino acid substitutions do not provide ample written description for the compounds since the claims do not describe a single structural feature.

11. As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claims 1, 39 and 49 are broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule that can form peptide bonds and make up the ghrelin like compounds (such as antagonists, agonists, variants and homologs). It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of organic molecules that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a peptide or a peptide-like molecule or other peptidic molecules and other synthetic peptide or peptide-like molecule that can form peptide bonds and act as ghrelin like compounds.

12. The specification is limited to the peptide or peptide-like molecules that belong to the same class of protein, ghrelin-like compounds having formula I, Z^1-$(X^1)_m$-(X^2)-$(X^3)_n$-Z^2 and the limitation wherein m is an integer in the range of from 1-10, n is 15-35, and

wherein (a) the ghrelin-like compound or pharmaceutically acceptable salt thereof is 27-28 amino acids in length. The specification discloses that "secretagogue" includes the naturally occurring 28 amino acid human ghrelin, the amino acid of which is shown in SEQ ID NO:1, as well as the naturally occurring 27 amino acid human ghrelin, the amino acid of which is shown in SEQ ID NO: 2, and the present invention relates to the use of ghrelin or a peptide homologous thereto (see paragraph [0359]). Furthermore, the reference discloses that the invention includes diastereomers as well as their racemic and resolved enantiomerically pure forms. Secretagogoues can contain, D-amino acids, L-amino acids, alpha-amino acid, beta-amino acid, gamma-amino acid, natural amino acid and synthetic amino acid or the like or a combination thereof. Preferably, amino acids present in a ghrelin-like compound are the L-enantiomer (see paragraph [0360]). The ghrelin-like compound preferably comprises an amino acid modified with a bulky hydrophobic group. The number of amino acids N-terminally to the modified amino acid is preferably within the range of from 1-9. Accordingly, m is preferably an integer in the range of from 1-9, 1-8, 1-7, 1-6…1-2 (see paragraph [0360]). The specification further discloses the possible X^1, X^2 and X^3 in the formula I (see paragraphs [0368] to [0375]). The specification further discloses SEQ ID NOS: 1-28 that includes from 1 amino acid (SEQ ID NO: 28) to 28 amino acids (SEQ ID NO:1). However, the recitation of the structure does not correlate with the sequences and preferred embodiment disclosed in the specification. For example, $(X^1)_m$ implies that when m is 5, and X^1 is Ser, then the sequence will be Z^1-Ser-Ser-Ser-Ser-Ser-(X^2)-$(X^3)_n$ - Z^2. The same situation arises with $(X^3)_n$: if X^3 is Gly, and n is 15, then the sequence will

be Z^1-$(X^1)_m$-(X^2)-$(Gly)_{15}$- Z^2.The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention of the formula I. The specification and claims recite that the compound is 27-28 amino acids in length and is at least 80% homologous to SEQ ID NO:1. However, SEQ ID NO:1 has the sequence GSSFLSPEHQRVQQRKESKKPPAKLQPR. If X^1 is G, and X^2 is S then X^3 must be SFLSPEHQRVQQRKESKKPPAKLQPR. However, this sequence does not correspond to the formula I. The working example describes the Ghrelin (1-9)-NH2, [Ser3(propionyl)]rGhrelin (1-28) synthesis (see Example 2) and using some of these ghrelin-like compound as subcutaneous administration to patients in need thereof (see Examples 6-12). The specification does not describe any other homologous of SEQ ID NO:1, such as derivatives, variants, and other modified amino acids, such as peptidomimetics that form peptide bonds. For example, as described above, 80% of SEQ ID NO: 1 (28 amino acids) means having at least 23 amino acid homologous to SEQ ID NO:1. Since there are 28 amino acids present in SEQ ID NO:1, this implies that there are 28*5= 140 different possibilities of available sequence variants. Even at 90% homologous to SEQ ID NO:1, this implies that there are 28*2=56 different sequence variants possible. Descriptions of SEQ ID NOS:1-28 are not sufficient to encompass numerous other proteins to the same genus. Further, some of the SEQ IDs disclosed do not further limit the broad claim 1. For example, SEQ ID NO:28 consists of amino acid Phe. The specification discloses that in a preferred embodiment (X1)m has a Gly residue in the N-terminal part of the sequence, and lists G, GS, GC, GK, GD, GE, GR, GH, GN, GQ, GT and GY. If for example, X^1 is G and X^2 is S and X^3 is F, then this GSF

sequence is only 10% sequence homologous to SEQ ID NO:1. The specification does not disclose the domains of the ghrelin amino acid sequence that is required to maintain its activity. Therefore, description of SEQ ID NOS: 1-28 are not sufficient to encompass numerous other proteins and compounds to the same genus. The conservative amino acid substitutions would imply that all 28 amino acids can be conservatively substituted. Therefore, there is more numbers of homolog possibilities. Furthermore, the specification discloses natural amino acid and synthetic amino acid or the like as long as the desired functional property is retained by the polypeptide (see paragraph [0077]). The only description of synthetic amino acid is by its "function" and no structural information is provided. Additionally, the specification discloses that bulky hydrophobic group is preferably acyl group, or a fatty acid (see for example paragraph [0020]). However, the specification does not describe or disclose all other possible bulky hydrophobic groups. Hydrophobic groups are anything that are resistant to or having a lack of affinity for water (see NPL-definition of hydrophobic.pdf). This means that any large lipophilic molecules such as alkanes, oils, fats are bulky hydrophobic groups. For example, there are varying lengths, varying amino acid compositions, and numerous distinct qualities that make up the genus. There are numerous compounds that make up the genus of bulky hydrophobic group. For example, there are varying lengths of carbon chains, different compositions, and different types of lipophilic compounds. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

13. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to Applicant's Arguments

14. Applicant argues that "specification discloses various truncated peptides on pages 40-43...set forth specific preferred $(X^1)_m$ sequences at p38, L25-29 (US 2007/0037751, paragraphs [0362]-[0363]), preferred X^2 at page 39, lines 7-10, preferred $(X^1)_m$-(X^2) sequences at lines 11-15; preferred (X^3) sequences at page 38, lines 21-27 and page 39, line 10 to page 43, line 26 (US 2007/0037751, paragraphs [0366]-[0375])…thus have disclosed, by complete structure, the sequences of at least three compounds which are within the scope of the generic claim." Applicant further argues that with regards with Ex parte Kubin, "…claims to DNAs encoding proteins with at least 80% identity to human NAIL were held unrepresentative of the claimed genus. But there, (1) the disclosed DNAs encoded fusion proteins all of which comprised just the mature human NAIL sequence, without variation (i.e., insofar as the NAIL protein

component was concerned, there was just a single complete structure), and (2) there was no guidance as to variation, e.g., identification of binding sites. Here first of all, clause (b) of claim 1 requires a higher percentage identity (90%) than does Kubin…the claim is supported by three different complete structures, whereas the claim in Kubin was supported by only one." Applicant further argues that "the written description should be acknowledged for the 90% identity, the 95% identity or the 98% identity. Moreover, new claim 49 deserves separate consideration…the permissible truncations are, as previously discussed, already limited by clauses (a) and (b): the ghrelin-like compound cannot be less than 25 a.a. and, since human ghrelin is 28 a.a., that means no more than three a.a. can be truncated."

15. Applicant's arguments have been fully considered but have not been found persuasive because claim 1 and 39 are to a genus of ghrelin-like compound that is at least 80% homologous and 90% homologous to SEQ ID NO:1. Furthermore, the newly added claims do not further define the structure of the ghrelin-like compounds. The specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of homologous peptides. The specification is not limited to polypeptides that share a common core. There is no disclosure a polypeptide with 80%-95% homology that has the capability of having the bioactivity as claimed. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than

outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Recently in *Ex Parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007), Board of Patents Appeals and Interferences, found lack of written description in a claim drawn to a genus of polynucleotides encoding polypeptides "at least 80% identical to amino acids 22-221 of SEQ ID NO:2" The Board stated:

> "Claim 73 is to a genus of polynucleotides encoding polypeptides "at least 80% identical to amino acids 22-221 of SEQ ID NO:2" which bind to CD48. Sufficient description to show possession of such a genus "may be achieved by means of a recitation of a representative number of cDNAs, defined by peptide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. See *University of Rochester*, 358F.3d at 927, 69 USPQ2d at 1895.
>
> In this case, Appellants have sequenced two nucleic acids falling within the scope of claim 73 and three fusion proteins whose nucleotide sequences would fall within the scope of claim 73. None of these sequences varies amino acids 22-221 of NAIL, and thus these sequences are not representative of the genus.
>
> Appellants also have described how to make and test other sequences within claim 73 sufficiently to satisfy the enablement requirement. **However, they have not described what domains of those sequences are correlated with the required binding to CD48, and thus have not described which of NAIL's amino acids can be varied and still maintain binding. Thus, under Lilly and its progeny, their Specification would not have shown possession of a sufficient number of sequences falling within their potentially large genus to establish possession of their claimed genus.** *Cf. Enzo*, 323 F.3d at 964, 63 USPQ2d at 1612 ("if the functional characteristic of…binding to [CD48] were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed," the written description requirement may be met).
>
> Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function...does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is"). "See *Kubin* at 1417.

Here, similar to Kubin, the specification fails to describe what domains of those sequences are correlated with the required activity, and thus have not described which of the SEQ ID NO:1 amino acids can be varied and still maintain binding. The instant specification does not disclose what domains are required for activity, and which amino acids can be varied and still maintain binding. Regarding claim 49, the claim recites that "the amino acid sequence of said ghrelin-like compound differs from that of human ghrelin solely by (1), (2) or (3) conservative amino acid substitution." Since there are 28 amino acids in human ghrelin, there are vast numbers of ghrelin-like compound that comprise the conservative amino acid substitutions. Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Rejection-35 U.S.C. 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1-3, 5-6, 13-18, 20, 22, 27-29, 31, 33-35, 39-40 and 43-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Bednarek MA (WO 01/92292 A2).

18. The instant claims are drawn to a method for prophylaxis or treatment of cancer cachexia in an individual in need thereof, comprising administration to the individual of a ghrelin-like compound or a pharmaceutically acceptable salt thereof, wherein the ghrelin-like compound comprises a structure defined by formula I, and wherein (a) said ghrelin-like compound or pharmaceutically acceptable salt thereof is 27-28 amino acids in lengths, with the proviso that said ghrelin-like compound is at least 80% homologous to SEQ ID NO:1.

19. Bednarek MA patent teaches truncated ghrelin analogs active at the GHS receptor and these analogs have a variety of different uses including being used as a research tool and being used therapeutically (see abstract). The reference further teaches SEQ ID NO:1 (the structure of human ghrelin with modified serines), and teaches that the core region at position 2 or 3 is modified with a bulky hydrophobic R group (p.3, lines 11-20). This meets the limitation of claims 1-3, 6, 13-14 and 39-40, since SEQ ID NO:1 of the reference is the same as the SEQ ID NO: 1 of instant claims, thus meeting the limitation of at least 80% sequence homology to SEQ ID NO:1. The reference further teaches a truncated ghrelin analog having a structure selected from the group consisting of Z^1-GSXF$(Z)_n$-Z^2 or Z^1-GXSF$(Z)_n$-Z^2, wherein Z1 is optionally present protecting group , Z2 is an optionally present protecting group, n is 0 to 19 or a pharmaceutically acceptable salt thereof (see p. 3, lines 21-32 and p. 4, lines 1-4) and teaches SEQ ID NO: 4 (p. 27, line 16) which is at least 80% of SEQ ID NO: 1 (i.e., 23 amino acids in lengths). This meets the limitation of claims 1-2, 6 and 39. Furthermore, the reference teaches that ghrelin agonists can be used to achieve a beneficial effect in

a subject (mammals, including a human, rat, a mouse, or a farm animal) such as one or more of the following: treating growth hormone deficient state, increasing muscle mass…facilitating weight gain, facilitating maintenance of weight, facilitation maintenance of physical function…facilitating appetite increase. Facilitating a weight gain, maintenance in weight, or appetite increase is particularly useful for a patient having a disease or disorder, or undergoing a treatment, accompanied by weight loss…anorexia, bulimia, cancer cachexia, AIDS, wasting, cachexia, and wasting in frail elderly. Examples of treatments accompanied by weight loss include chemotherapy, radiation therapy, temporary or permanent immobilization, and dialysis (see p. 5, lines 23-35 and p. 6, lines 1-6). This reads on claims 27-29, 31, 33-35, 39-40 and 44, since lipodystrophy (loss of fat from one area due to multiple injections at the same site) can be a possible side effect of antiretroviral drugs. Furthermore, the Applicant has pointed out that the treatment is directed to cancer cachexia, a condition not dependent on cancer type (see Applicant's election with traverse, p. 4). Furthermore, since the reference discloses that the treatments accompanied by weight loss include chemotherapy, radiation therapy, and since cancer is being treated along with cancer cachexia, this reads on claims 33-35. The reference further teaches that the ghrelin analog can be administered by nasal aerosol or inhalation formulations may be prepared, for example, as solutions in saline, and in intravenous (both bolus and infusion), intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscularly. When administered by injection, the injectable solution or suspension may be formulated using suitable non-toxic, parenterally acceptable diluents or

solvents, such as Ringer's solution or isotonic sodium chloride solution, or suitable dispersion or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid (see p. 15, lines 9-20). This reads on claims 15-18. Furthermore, the reference teaches that truncated ghrelin analogs can be provided in a kit, such a kit typically contains an active compound in dosage forms for administration (see p. 15, lines 30-31). This further reads on claim 16, since the reference teaches that an injectable solution or suspension may be formulated using suitable non-toxic solvents. The reference further teaches that the daily dose for a subject is expected to be between 0.01 mg (10 μg) and 1000 mg per subject per day (see p. 15, lines 28-29), which reads on claims 20, 22 and 43. The reference teaches the 28mer ghrelin analogs, thus this reads on claims 3, 14, 39, 40, 45, 50-52. The reference further teaches that the EC_{50} of the ghrelin analogs are less than 500 nM (for example, SEQ ID NO:7 had EC_{50} of 18±0.9 nM, see Tables 1-3), thus meets the limitation of claim 46. Please note that the instant specification discloses EC_{50} not ED_{50} (see paragraph [0389]). Further, the reference teaches ghrelin analog has at least 50% of the activity of wild-type human ghrelin (see column 7, lines 9-20), meeting the limitation of claim 48. The reference teaches SEQ ID NO:4 that is at least 80% homologous to instant SEQ ID NO:1, that comprises C-terminal truncation (see Claim 11), meeting the limitation of claim 49. The reference teaches that the core region at position 2 or 3 is modified with a bulky hydrophobic R group (p.3, lines 11-20). The sequences show that the 2^{nd} or 3^{rd} position amino acid is a serine residue that is modified, which is meets the limitation of claim 5.

Response to Applicant's Arguments

20. Applicant argues that "there are two reasons why Bednarek's teachings concerning human ghrelin cannot be considered anticipatory of the present method claims. Bednarek also discloses certain truncated ghrelin analogs. The term "have" depending on context, can be "open" or "closed". Applicant indicates that "we argued that Bednarek's "have" or "having" must be interpreted as "closed" because he teaches that "the smaller size of truncated ghrelin analogues offers advantages over longer-length ghrelin…" Applicant argues that "the PTO instructs applicants not to show the terminal NH2- and –COOH in a sequence identified by SEQ ID NO:" and "the terminal NH2- and –COOH are recited in the structure of Bednarek page 6, specifically in the definitions of Z1 and Z2 at lines 32-35…Bednarek does not disclose ghrelin analogues longer than 23 a.a." Furthermore, Applicant argues that "paragraph (b) requires that it be at least 90% homologous, i.e., at least (nominally) "25.2" amino acids. Both paragraphs (a) and (b) thus exclude Bednarek's truncated ghrelin analogs".

21. Applicant's arguments have been fully considered but have not been found persuasive because Bednarek reference teaches the ghrelin "analogs" claimed in the instant application. Bednarek patent teaches 28mer ghrelin analogs (see for example, SEQ ID NO: 7), that meets the limitation of at least 80% homologous to instant SEQ ID NO:1. The 23mer (SEQ ID NO:4) claimed in Bednarek's claim 11 meets the limitation of at least 80% homology to instant SEQ ID NO:1, since 28X0.8=22.4 (i.e., 23mer has to be homologous). Bednarek discloses SEQ ID NOS: 1, 7-21 that are all 28mers, teaching at least 80% homology to instant SEQ ID NO:1. Furthermore, the reference

teaches SEQ ID NO:7 having a fatty acid modified Ser at the 3rd position. This meets the limitation of at least 98% homologous, since the instant application has not defined what the fatty acid modifies the amino acid. In regards to the "open" and "closed" language of Bednarek's sequences, as disclosed in claim 11, SEQ ID NOS: 4-5, and 6 show that the C-terminal ends are protected with an NH group. As indicated from the Bednarek formula, Z^1-GSXF$(Z)_n Z^2$ and Z^1-GXSF$(Z)_n Z^2$, wherein Z^1 and Z^2 are optionally present protecting groups. Therefore, if they are both absent, both N- and C-terminal ends can have further amino acid additions.

Rejection-35 U.S.C. 103

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

24. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

25. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bednarek MA (WO 01/92292 A2) as applied to 1-3, 5-6, 13-18, 20, 22, 27-29, 31, 33-35, 39-40 and 43-45-52 above, and further in view of Okamoto T (International Journal of Molecular Medicine, 2002, 9: 369-372).

26. The instant claims are drawn to a method for prophylaxis or treatment of cancer cachexia in an individual in need thereof, comprising administration to the individual of a ghrelin-like compound or a pharmaceutically acceptable salt thereof, wherein the ghrelin-like compound comprises a structure defined by formula I, and wherein (a) said ghrelin-like compound or pharmaceutically acceptable salt thereof is 27-28 amino acids in lengths, with the proviso that said ghrelin-like compound is at least 80% homologous to SEQ ID NO:1. The claims are further drawn to the method further comprising administration of an effective amount of an NSAID medicament.

27. The teachings of Bednarek are described supra. The difference between the reference and the instant claims is that the reference does not teach further administration of NSAID medicament for treating cancer cachexia.

28. However, Okamoto T teaches that zaltoprogen (a non-steroidal anti-inflammatory drug) causes potent inhibition of cyclooxygenase-2 with fewer side effects on the gastrointestinal tract. Zaltoprofen improves the loss in body weight in both Con A-treated mice and carbon tetrachloride-treated rats. These results suggest the possible application of zaltoprogen for the treatment of sickness behaviors including loss of body weight occurring in cancer cachexia (see abstract, p. 370, left and right columns and conclusion, pp. 370-371). The reference further discloses that administration of aspirin or indomethacin prolongs the survival of patients with esophageal cancer, stomach cancer, and rectal cancer. The mechanism underlying the ability of NSAIDs to prolong the survival of cancer patients is not known, but the present results with zaltoprofen improves the body weight loss in rodent sickness behavior model, suggest protection against wasting (see p. 371, right column, 1st paragraph).

29. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Bednarek and Okamoto since both prior arts teach treating cancer cachexia. There is a reasonable expectation of success, since zaltoprofen protects against wasting in cancer and behavior sickness models and ghrelin analogs are effective in facilitating a weight gain, maintenance in weight or appetite increase in patients having a disease or disorder. Furthermore, the MPEP states the following:

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....Appellant argues... hindsight reconstruction or at best,... obvious to try'.... We agree with appellant."). Since Bednarek teaches using ghrelin analog to treat cancer cachexia and Okamoto teaches using NSAID to treat cancer cachexia, there is a

reasonable expectation of success, since combining the two compounds would at least have an additive effect.

Response to Applicant's Arguments

30. Applicant argues that "Okamoto is cited merely to show administration of an NSAID (zaltoprogen) and does not remedy the deficiencies of Bednarek."

31. Applicant's arguments have been fully considered but have not been found persuasive because the combination of Bednarek reference and Okamoto reference teach the instantly claimed invention. As described above, Bednarek teaches administration of ghrelin analog to treat cancer cachexia; Okamoto teaches using HSAID (zaltoprogen) to treat cancer cachexia. It would have been obvious to combine the two compounds that are used to treat the same disease or disorder (cancer cachexia) to form a third composition to be used for the treatment of cancer cachexia, since the combining the two compounds would at least have an additive effect.

32. Claims 19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bednarek MA (WO 01/92292 A2) as applied to 1-3, 5-6, 13-18, 20, 22, 27-29, 31, 33-35, 39-40 and 43-45-52 above.

33. The instant claims are drawn to a method for prophylaxis or treatment of cancer cachexia in an individual in need thereof, comprising administration to the individual of a ghrelin-like compound or a pharmaceutically acceptable salt thereof, wherein the ghrelin-like compound comprises a structure defined by formula I, and wherein (a) said ghrelin-like compound or pharmaceutically acceptable salt thereof is 27-28 amino acids

in lengths, with the proviso that said ghrelin-like compound is at least 80% homologous to SEQ ID NO:1. The claims are further drawn to the method wherein the medicament is administered prior to or during a meal and the method wherein the medicament is administered as a bolus prior to or during a meal, said bolus comprising an amount of ghrelin-like compound of a salt thereof equivalent to from 0.3 μg to 600 mg ghrelin.

34. The teachings of Bednarek are described supra. The difference between the reference and the instant claims is that the reference does not teach when the medicament is administered.

35. However, it would have been obvious to one of ordinary skill in the art to try different time points of administering the medicament. It has been held that under KSR that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in KSR, When there is motivation "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727,_,82 USPQ2d 1385, 1397 (2007).

36. The "problem" facing those in the art was when to administer the medicament to achieve the optimal conditions for the treatment of cancer cachexia (facilitate weight gain, maintenance of weight, facilitate appetite increase, etc), and there were a limited number of methodologies available to do so, for example Bednarek discloses that daily

dose for a subject is expected to be between 0.01 mg (10 μg) and 1000 mg per subject per day and a desirable effect can be obtained when administered to a subject during regular intervals, such as 1 to 6 times a day, during the course of 1 or more days, and the kit contains instructions indicating the use of the dosage form to achieve a desirable affect and the amount of dosage form to be taken over a specified time period (see pp. 15-16, WO 01/92292 A2). The skilled artisan would have had reason to try different time points and before, after and during a meal of administration of the medication methodologies with the reasonable expectation that at least one would be successful. Since the ghrelin analogs can be used to facilitate a weight gain, maintain weight and facilitate appetite increase in patients suffering from bulimia, cancer cachexia, AIDS, wasting cachexia and wasting in frail elderly, thus, administering ghrelin analogs prior to meal or during a meal for treating cancer cachexia in the dosage claimed is a "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

Response to Applicant's Arguments

37. Applicant argues that "this rejection does not address the issue that Bednarek advocates a more drastic truncation than that is permitted by applicant's claim 1."

38. Applicant's arguments have been fully considered but have not been found persuasive because Bednarek teaches ghrelin analogs that are at least 80% homolog to the instant SEQ ID NO:1. Therefore, as described above in the rejection, it would have been obvious to one of ordinary skill in the art to try different time points of administering

the medicament. The skilled artisan would have had reason to try different time points and before, after and during a meal of administration of the medication methodologies with the reasonable expectation that at least one would be successful. Since the ghrelin analogs can be used to facilitate a weight gain, maintain weight and facilitate appetite increase in patients suffering from bulimia, cancer cachexia, AIDS, wasting cachexia and wasting in frail elderly, thus, administering ghrelin analogs prior to meal or during a meal for treating cancer cachexia in the dosage claimed is a "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

Conclusion

39. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654

/Anish Gupta/
Primary Examiner, Art Unit 1654